

## REMARKS

Upon entry of this amendment, claims 1, 10-13, 15, 29-31 and 33-42 are pending in the instant application. Claims 1, 10-13, 15, 29 and 31 have been amended, and claims 33-42 have been added. The present amendments are fully supported by the specification and the claims as originally filed. For example, support for the term "an adenovirus vector comprising a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide" appears at least at page 26 in Example 1. Support for the term "a route selected from the group consisting of intraperitoneal, subcutaneous, nasal, intravenous, oral and transdermal delivery" can be found at least at page 5, line 28 through page 6, line 2; at page 7, line 26 through page 8, line 1; at page 22, lines 19-21; and in the claims as originally filed. Support for the term "a method of inducing a pancreatic islet gene expression profile" can be found at least at page 11, line 18 through page 12, line 7. Support for the term "mammal" can be found at least at page 6, lines 11-12.

Support for the terms "a method of inducing insulin expression in the liver of a mammal" and "a method of inducing insulin expression in a liver cell" can be found at least at pages 26-27, in Example 2. Support for the terms "a method of inducing somatostatin expression in the liver of a mammal" and "a method of inducing somatostatin expression in a liver cell" can be found at least at page 27-28, in Example 3. Support for the terms "a method of inducing glucagon expression in the liver of a mammal" and "a method of inducing glucagon expression in a liver cell" can be found at least at page 28, in Example 4. Support for the terms "a method of inducing prohormone convertase 1/3 (PC 1/3) expression in the liver of a mammal" and "a method of inducing prohormone convertase 1/3 (PC 1/3) expression in a liver cell" can be found at least at page 28, in Example 5. No new matter has been added.

Applicant notes that several of the pending claims (*i.e.*, claims 29 and 37-41), as amended herein, recite methods for inducing selected pancreatic hormone expression or pancreatic islet gene expression in a liver cell. Applicant believes that these claims fall within the elected invention.

### ***Election/Restriction***

Applicant notes with appreciation that the Examiner has withdrawn the election requirement regarding two species of the present invention – the routes of delivery and the hormones induced. Claim 15 has been amended accordingly in light of this withdrawal.

### ***Specification***

The Examiner asserts that the “nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821-1.825.” (Office Action at p. 3). Applicant notes that the specification has been amended herein to ensure that the oligonucleotides disclosed in the specification correspond to the specific SEQ ID NOs disclosed in the raw sequence listing submitted on October 19, 2001 as Paper No. 9. In light of the amendments made herein, Applicant believes that the nucleotide sequence disclosure contained in the above-identified application complies with the requirements for such a disclosure. Accordingly, Applicant respectfully requests that the Examiner withdraw this objection.

### ***Claim Objections***

The Examiner has objected to claims 1, 16, 24 and 29, because these independent claims “encompass delivery of any type of compound, not only a polynucleotide,” while the “elected invention is drawn to delivery of a polynucleotide.” (Office Action at p. 4). Applicant notes that independent claims 16 and 24 (and the claims dependent therefrom) have been canceled, thereby rendering moot any objection to these claims. Moreover, claims 1 and 29, as amended herein, are directed to methods that encompass the delivery of a polynucleotide in the form of an adenovirus vector. Likewise, the additional independent method claims presented herein (*i.e.*, claims 33-41) are also directed to methods that encompass the delivery of a polynucleotide, rather than the delivery of “any type of compound.” Therefore, the pending independent claims are clearly directed to elected invention, and Applicant respectfully requests that the Examiner withdraw this objection.

## *Claim Rejections Under 35 USC § 112*

### **Rejections Under 35 USC § 112, First Paragraph**

Claims 1, 2, 9-13, 15-17, 24 and 26-32 stand rejected under 35 USC 112, first paragraph, for lack of enablement. According to the Examiner:

[T]he specification, *while being enabling for a method of increasing insulin, somatostatin, glucagon and prohormone convertase 1/3 gene expression in the liver of mammals comprising administering AdCMVPDX-1 in an amount effective enough to obtain PDX expression in the liver of said mammal*, does not reasonably provide enablement for use of other delivery vehicles, inducing any and all pancreatic hormones, or providing a therapeutic affect [sic] to a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. (Office Action at p. 4-5) (emphasis added).

Applicant traverses this rejection. Claims 2, 9, 16-17, 24, 26-28 and 32 have been canceled, thereby rendering moot any rejections regarding these claims. Moreover, independent claim 1 (and its dependent claims) have been amended as suggested by the Examiner to recite a method of inducing the expression of a pancreatic hormone selected from the group consisting of insulin, somatostatin, and glucagon in the liver of a mammal. The method recited by claim 1 comprises the step of administering to the mammal an adenovirus vector comprising a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount sufficient to induce said pancreatic hormone expression in said liver in said mammal.

Similarly, independent claim 29 (and its dependent claim) has been amended to recite a method of inducing a pancreatic islet gene expression profile in a liver cell of a subject. The method according to claim 29 comprises the step of administering to the subject an adenovirus vector comprising a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount sufficient to induce said pancreatic islet gene expression in said liver cell in said subject.

New claims 33-36 are directed to methods of inducing the expression of insulin, somatostatin, glucagon, or prohormone convertase 1/3 (PC 1/3) in the liver of a mammal by administering to the mammal an adenovirus vector comprising a cytomegalovirus (CMV)

promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide in an amount sufficient to induce said selected expression in said liver of said mammal. Likewise, new claims 37-41 are directed to methods of inducing the expression of insulin, somatostatin, glucagon, or prohormone convertase 1/3 (PC 1/3) in a liver cell by contacting the cell with an adenovirus vector comprising a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, thereby inducing said selected expression in said liver cell.

Claim 31 has been amended to recite a composition comprising, in an amount effective to induce pancreatic hormone expression in a liver cell, a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, and a carrier. Claim 42 is directed to a composition that includes an adenovirus vector having a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, and a carrier.

Thus, the pending claims are not directed to the use of "other delivery vehicles" for delivering a PDX polynucleotide to a subject. Rather, claims 1, 10-13, 15, 29-31 and 33-42 are directed to methods and compositions that use an *adenovirus vector* having a CMV promoter as a delivery vehicle for a polynucleotide encoding a PDX-1 polypeptide. Furthermore, the pending claims, and in particular, the pending method claims, are not directed to methods of inducing "any and all pancreatic hormones." Independent claims 1, 31 and 33-41 (and their respective dependent claims, if any) recite methods of inducing *selected* expression of insulin, somatostatin, glucagon, or prohormone convertase 1/3 (PC 1/3). Moreover, the pending claims, particularly the method claims, are not directed to methods for "providing a therapeutic [effect] to a subject." Each of these method claims (*i.e.*, claims 1, 29, 31 and 33-41) simply recites a method of inducing a selected pancreatic hormone expression or pancreatic islet gene expression profile in a liver cell or in the liver of a mammal by administering a recombinant adenovirus vector. Thus, these claims are *not* directed to methods for providing a therapeutic effect.

The specification of the present application enables any person skilled in the art to make and use Applicant's invention commensurate in scope with the pending claims without undue experimentation. For example, the specification contains numerous working examples detailing how to make and use the claimed adenovirus vector having a CMV promoter that is operably linked to a polynucleotide encoding a PDX-1 polypeptide. (*See e.g.*, Example 1 at page 26

(describing the construction of the claimed recombinant adenovirus vector); and Examples 2-5 at pages 26-28 (illustrating the induction of endogenous insulin, somatostatin, glucagon and prohormone convertase 1/3 expression in the liver of mice through the use of the claimed recombinant adenovirus vector)). Therefore, the pending claims as amended, which are *not* directed to the delivery of any vector system, to the induction of any pancreatic hormone, or to the treatment of any pancreatic-related disorder, are clearly enabled by the teachings and guidance in these working examples, and throughout the specification.

In fact, the Examiner acknowledges that the pending claims are enabled. At page 4, lines 16-19 of the Office Action, the Examiner explicitly states that the present specification is enabling "for a method of increasing insulin, somatostatin, glucagon and prohormone convertase 1/3 gene expression in the liver of mammals comprising administering AdCMVPDX-1 in an amount effective enough to obtain PDX expression in the liver of said mammal." Therefore, Applicant respectfully requests that the Examiner withdraw this rejection.

Applicant notes that several claims are directed to methods of inducing selected pancreatic hormone expression in a liver cell. These claims, however, are also enabled by the teachings and guidance of the present specification. As described above, the specification is enabling for methods of inducing pancreatic hormone expression or pancreatic islet gene expression profile *in the liver of a mammal*. Therefore, the specification is also inherently enabling for methods that induce pancreatic hormone expression or pancreatic islet gene expression *in a liver cell*. To state the obvious, an assertion that "the liver" expresses pancreatic hormones, such as insulin, glucagon, or somatostatin, is actually an assertion that at least one liver cell is producing and secreting the polypeptides that comprise pancreatic hormones. Accordingly, a specification that is enabling for methods of inducing pancreatic hormone expression or pancreatic islet gene expression in "the liver," is also enabling for liver cells. The Examiner should withdraw all rejections under 35 USC § 112, first paragraph.

#### **Rejections Under 35 USC § 112, Second Paragraph**

Claims 1, 2, 9-13, 15-17, 24 and 26-32 stand rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner has concluded that "[c]laim 1, 16, 24 and 29 is vague and unclear in what disorder is being treated."

Applicant traverses. The pending claims as amended are not drawn to the delivery of a PDX polynucleotide to a subject in need of increased PDX. As amended, these claims are not directed to "a patient in need," or "a therapeutic amount," or even to the treatment of a particular disorder. Rather, the pending claims, and in particular, the pending method claims, are directed to an adenovirus vector having a CMV promoter operably linked to a PDX polynucleotide, wherein the adenovirus vector can be used to induce pancreatic hormone expression or pancreatic islet gene expression profiles in a liver cell or in the liver of a mammal. As these claims are not directed to the use of the adenovirus vector in the treatment of any disorder, the Examiner's rejection has been rendered moot. Applicant, therefore, respectfully requests that the Examiner withdraw this rejection as well.

### ***Claim Rejections Under 35 USC § 102***

#### **Rejection of Claim 31 Under 35 USC § 102(b) in view of Milewski**

Claim 31 has been rejected under 35 USC 102(b) as being anticipated by the teachings of Milewski *et al.*, 139(3) Endocrinology 1440-49 (1998) ("Milewski"). In particular, the Examiner asserts that Milewski teaches "vectors containing the polynucleotide sequences which encode PDX which can be delivered to cells to meet each of the limitations set forth in the claim." (Office Action at pp. 12-13).

Applicant traverses this rejection, as claim 31 has been amended herein to recite a composition comprising, in an amount *effective to induce pancreatic hormone expression in a liver cell*, a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, and a carrier. In contrast, Milewski fails to disclose or suggest a composition that is effective to induce pancreatic hormone expression in a liver cell, as recited by amended claim 31. Milewski, therefore, does not teach every limitation recited by claim 31. As claim 31 is not anticipated by this reference, Applicant respectfully requests that the Examiner withdraw this rejection.

Applicant notes that new claim 42 is also not anticipated by Milewski. Claim 42 is directed to a composition comprising "an *adenovirus vector* comprising a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide" and a carrier. In contrast, the vectors disclosed by Milewski are not *adenovirus vectors*. Moreover, Milewski fails to teach or suggest a pharmaceutical composition comprising an *adenovirus vector* containing a CMV promoter that is operably linked to a

polynucleotide sequence encoding a PDX-1 polypeptide. Thus, this reference fails to disclose every element recited by new claim 42. Accordingly, claim 42 is not anticipated by Milewski.

**Rejection of Claim 31 Under 35 USC § 102(b) in view of Marshak**

Claim 31 also stands rejected under 35 USC §102(b), as being anticipated by Marshak *et al.*, 93 Proc. Natl. Acad. Sci. U.S.A. 15057-62 (1996) ("Marshak"). According to the Examiner:

Marshak *et al.* teach that a variety of factors affect the expression of [glucose sensitive factor] (GSF), among those high glucose levels are demonstrated to increase the expression of GSF/PDX and increase the promoter activity in reporter assays (see for example results in Figure 2). In light of the evidence that glucose increases the expression and activity of PDX, glucose would meet the limitation set forth in the claim. (Office Action at p. 13).


Applicant traverses this rejection as well. As discussed above, claim 31 has been amended to recite a composition comprising, in an amount *effective to induce pancreatic hormone expression in a liver cell*, a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide, and a carrier. Marshak, in contrast, fails to disclose or suggest a composition that is effective to induce pancreatic hormone expression in a liver cell, as recited by claim 31. Marshak, therefore, fails to disclose every limitation set forth in amended claim 31. Accordingly, claim 31 is not anticipated by this reference, and Applicant respectfully requests that the Examiner withdraw this rejection as well.

New claim 42 is also not anticipated by Marshak. As described above, new claim 42 is directed to a composition comprising "an *adenovirus vector* comprising a cytomegalovirus (CMV) promoter operably linked to a nucleic acid encoding a pancreatic and duodenal homobox 1 (PDX-1) polypeptide" and a carrier. Marshak, in contrast, fails to teach or suggest the use of a composition that contains *any* adenovirus vector, let alone an adenovirus vector having a CMV promoter that is operably linked to a polynucleotide sequence encoding a PDX-1 polypeptide. Marshak, therefore, fails to disclose every limitation set forth in new claim 42. Accordingly, claim 42 is not anticipated by this reference.

## CONCLUSION

On the basis of the foregoing amendments and arguments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

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